Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial

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Summary

Background Head-to-head trials in psoriatic arthritis are helpful in guiding clinical decision making. The EXCEED study evaluated the efficacy and safety of secukinumab versus adalimumab as first-line biological monotherapy for 52 weeks in patients with active psoriatic arthritis, with a musculoskeletal primary endpoint of American College of Rheumatology (ACR) 20 response.

Methods This parallel-group, double-blind, active-controlled, phase-3b, multicentre (168 sites in 26 countries) trial enrolled patients aged at least 18 years with active psoriatic arthritis. Eligible patients were randomly assigned (1:1) by means of interactive response technology to receive secukinumab or adalimumab. Patients, investigators, site personnel, and those doing the assessments (except independent study drug administrators) were masked to study assignment. 300 mg secukinumab was administered subcutaneously at baseline, weeks 1, 2, 3, and 4, and then every 4 weeks until week 48 as a pre-filled syringe. Adalimumab was administered every 2 weeks from baseline until week 50 as 40 mg per 0·4 mL citrate free subcutaneous injection. The primary outcome was the proportion of patients with at least 20% improvement in the ACR response criteria (ACR20) at week 52. Patients were analysed according to the treatment to which they were randomly assigned. Safety analyses included all safety data reported up to and including the week 52 visit for each patient who received at least one dose of study drug. The trial is registered at ClinicalTrials.gov, NCT02745080.

Findings Between April 3, 2017 and Aug 23, 2018, we randomly assigned 853 patients to receive secukinumab (n=426) or adalimumab (n=427). 709 (83%) of 853 patients completed week 52 of the study, of whom 691 (81%) received the last study treatment at week 50. 61 (14%) of 426 patients in the secukinumab group discontinued treatment by week 52 versus 101 (24%) of 427 patients in the adalimumab group. The primary endpoint of superiority of secukinumab versus adalimumab for ACR20 response at week 52 was not met. 67% of patients in the secukinumab group achieved an ACR20 response at week 52 versus 62% of patients in the adalimumab group (OR 1·30, 95% CI 0·98–1·72; p=0·0719). The safety profiles of secukinumab and adalimumab were consistent with previous reports. Seven (2%) of 426 patients in the secukinumab group and six (1%) of 427 patients in the adalimumab group had serious infections. One death was reported in the secukinumab group due to colon cancer and was assessed as not related to the study drug by the investigator.

Interpretation Secukinumab did not meet statistical significance for superiority versus adalimumab in the primary endpoint of ACR20 response at week 52. However, secukinumab was associated with a higher treatment retention rate than adalimumab. This study provides comparative data on two biological agents with different mechanisms of action, which could help guide clinical decision making in the management of patients with psoriatic arthritis.

Funding Novartis Pharma.

Introduction

Psoriatic arthritis is clinically heterogeneous, comprising musculoskeletal and dermatological manifestations that might involve arthritis, spondylitis, enthesitis, dactylitis, and psoriasis of skin and nails, and is associated with impaired physical function and poor quality of life.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are typically the first choice in treating psoriatic arthritis symptoms, but have associated safety issues of cardiovascular risk and gastrointestinal toxicity; therefore, physicians initiate conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), preferably methotrexate, early in patients with poor prognostic factors and relevant skin involvement to modify underlying musculoskeletal and skin inflammation.[2,3]

Several biological disease modifying anti-rheumatic drugs (bDMARDs) targeting inflammatory cytokines are recommended for patients with psoriatic arthritis with inadequate response to csDMARDs.[3,4] Adalimumab, a human monoclonal antibody against tumour necrosis

Research in context

Evidence before this study

Many patients with psoriatic arthritis who have active psoriasis and musculoskeletal symptoms show inadequate clinical responses to conventional synthetic disease-modifying antirheumatic agents (csDMARDs), including methotrexate, in all manifestations of psoriatic arthritis, including arthritis, spondylitis, enthesitis, dactylitis, and psoriasis. Several biological disease-modifying anti-rheumatic drugs (bDMARDs) that target different inflammatory cytokines are recommended for patients with psoriatic arthritis with inadequate response to csDMARDs. Adalimumab, a human monoclonal antibody against tumour necrosis factor (TNF), is widely used as a first-line bDMARD in the treatment of patients with psoriatic arthritis in monotherapy or in combination with methotrexate. We searched PubMed using the terms "psoriatic arthritis", "biologic", and "head-to-head" for English language articles published from inception up to Jan 13, 2020, with no limitation or restriction for year of publication or article type. The search results yielded 30 articles, of which nine used matching adjusted indirect comparisons to compare two biologicals, 20 were review articles, and one was a head-to-head comparison of two biologicals in psoriatic arthritis. However, matching adjusted indirect comparisons have an inherent limitation of the methodology used and might lead to different conclusions; therefore, prospective head-to-head trials in psoriatic arthritis are needed to help guide physicians in clinical decision making. A 2020 head-to-head, open label, 24-week trial compared the efficacy and safety of two biologicals—adalimumab and ixekizumab (an IL-17A inhibitor)—in psoriatic arthritis and supported that ixekizumab was superior to adalimumab in achieving combined American College of Rheumatology 50 (ACR50) and Psoriasis Area and Severity Index 100 responses at week 24.

Added value of this study

To our knowledge, EXCEED is the first fully blinded head-to-head trial to evaluate the efficacy and safety of secukinumab (an IL-17A inhibitor) versus adalimumab (an anti-TNF agent) as first-line biological monotherapy in patients with active psoriatic arthritis with a musculoskeletal primary endpoint of ACR20 at week 52. The efficacy data in this study suggest that secukinumab was at least as efficacious as adalimumab in improving musculoskeletal endpoints, provided better responses on skin endpoints, and had a higher retention rate at week 52. No new safety signals were reported for secukinumab and adalimumab.

Implications of all the available evidence

This study presents a considerable volume of comparative efficacy and safety data on two biologicals with different mechanisms of action in the treatment of patients with psoriatic arthritis.

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factor (TNF), is widely used as a first line bDMARD in the treatment of patients with psoriatic arthritis as monotherapy or an add-on to methotrexate.[5] Secukinumab, a human monoclonal antibody that directly inhibits IL-17A, has shown substantial improvement in the key clinical domains of psoriatic arthritis, including signs and symptoms, radiographic progression, physical functioning, and quality of life.[6–8] In the treatment of patients with moderate to severe psoriasis and plaque psoriasis, secukinumab has shown greater efficacy versus a TNF inhibitor (etanercept) and an IL-12/23 inhibitor (ustekinumab).[9–11]

Both adalimumab and secukinumab are approved for treatment of patients with active psoriatic arthritis with or without the use of concomitant methotrexate.[5,6,12] More than 40% of patients treated with methotrexate discontinue treatment or are non-compliant because of poor tolerability or toxicity, or cannot receive methotrexate because of liver abnormalities related to psoriatic arthritis or concomitant alcohol abuse.[13–15] The European League Against Rheumatism (EULAR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations differ. EULAR proposes a treatment algorithm, whereas GRAPPA proposes an evidence-based clinical domain approach that includes biologicals with novel mechanisms of action.[3,16] However, there is a paucity of trials to determine which biological treatment should be the initial treatment in patients with psoriatic arthritis upon csDMARD failure or intolerance. The advent of biological therapies with selective mechanisms of action that are approved and widely used in clinical practice has prompted indirect comparison approaches to guide therapy, but these comparisons have methodological limitations.[17]

Head-to-head trials have shown that IL-17A inhibitors have higher efficacy in treatment of patients with moderate to severe psoriasis and on the skin manifestations of patients with psoriatic arthritis. However, comparative data are lacking on the efficacy of these drugs on musculoskeletal manifestations of psoriatic arthritis and are urgently required. The aim of the EXCEED study was to investigate whether secukinumab 300 mg monotherapy was superior to adalimumab 40 mg monotherapy as first-line bDMARD treatment, thus testing the musculoskeletal endpoint of the American College of Rheumatology (ACR) 20 response as the primary objective in a fully blinded manner. Safety of secukinumab and adalimumab was also assessed.

Methods

Study design and participants

EXCEED is a randomised, double-blind, active-controlled, phase-3b, multicentre (168 sites in 26 countries; appendix p 19), parallel-group, 52-week study that evaluated secukinumab monotherapy and adalimumab monotherapy in patients with active psoriatic arthritis who were naive to biological therapy for psoriatic arthritis and

See Online for appendix

psoriasis, and who were intolerant or had an inadequate response to csDMARDs.

Patients fulfilling all the following criteria were included in the study: aged at least 18 years of age, fulfilled the Classification Criteria for Psoriatic Arthritis,[18] had active psoriatic arthritis (defined as ≥3 swollen joints and ≥3 tender joints), had active plaque psoriasis with at least one plaque of at least 2 cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis, were naive to treatment with biologicals, had previously been treated with csDMARDs (including but not limited to methotrexate) with an inadequate response or had stopped treatment due to safety or tolerability problems, and had a previous inadequate response to NSAIDs for at least 4 weeks before randomisation.

Patients had to stop any csDMARD, including methotrexate, before randomisation, with a washout period of 4 weeks for all csDMARDs or 8 weeks for leflunomide. Patients who were receiving concomitant corticosteroids were required to be on a stable dose of 10 mg/day or less of prednisone or equivalent for at least 2 weeks before randomisation and remain on a stable dose up to week 52 (appendix p 13).

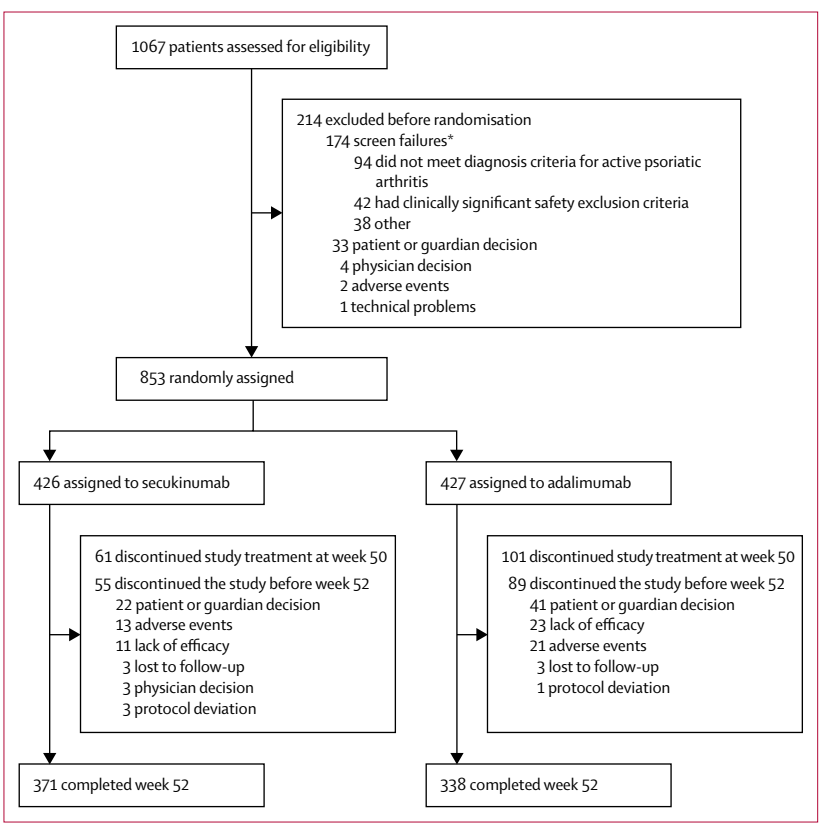

Figure 1: **Trial profile**
For the secukinumab group, six patients who discontinued treatment but stayed in the study up to week 52 are not included in the 55 patients who discontinued the study. For the adalimumab group, 12 patients who discontinued treatment but stayed in the study up to week 52 are not included in the 89 patients who discontinued the study. *Patients might have had multiple reasons for being a screen failure but are only counted for the first major reason in one of the three categories of screen failures

Key exclusion criteria were pregnancy, evidence of ongoing infection or malignancy, previous exposure to any biologicals or opioids, ongoing use of oral or topical retinoids, photochemotherapy, phototherapy, or topical skin treatment. For detailed information on the exclusion criteria, please refer to the appendix (p 14).

All clinical studies were done in compliance with the Declaration of Helsinki, International Council for Harmonization Guidelines for Good Clinical Practice, and local country regulations. All patients provided written informed consent to participate in the respective studies. The institutional review board at each participating centre approved the protocol.

Randomisation and masking

After a screening period of up to 8 weeks, eligible patients were randomly assigned (1:1) by means of interactive response technology to receive secukinumab or adalimumab. The interactive response technology assigned a randomisation number to the patient (randomisation block size was 4), which linked the patient to a treatment group and specified a unique medication number. The randomisation scheme for patients was reviewed and approved by a member of the Novartis randomisation office.

To maintain allocation concealment, all groups received placebo injections to ensure a consistent number of injections at each visit. Study treatments were administered by suitably qualified independent study drug administrators, who were not masked and had no responsibility for any aspect of patient assessment or follow-up. Before administration of study treatment, unmasked site personnel were required to use physical barriers (curtains, blindfolds, or similar measures) to prevent patients from seeing their study treatment to preserve the masking. Patients, investigators, site personnel, and those performing the assessments (except independent study drug administrators) were masked to the study assignment (appendix p 16).

Procedures

Secukinumab 300 mg was administered at baseline, weeks 1, 2, 3, and 4, and then every 4 weeks until week 48. Adalimumab 40 mg was administered every 2 weeks from baseline until week 50 (appendix p 19). Secukinumab was administered with a pre-filled syringe and adalimumab as 40 mg in 0·4 mL citrate free subcutaneous injection. Additional information about the assessments undertaken during the trial is provided in the appendix (p 17). Key efficacy (assessed by primary endpoint, key secondary endpoints, and other relevant exploratory endpoints), safety, and tolerability (assessed by adverse events, laboratory values, injection site reaction, and immunogenicity) assessments were done at screening, baseline, week 2, week 4, and every 4 weeks until week 52 (primary endpoint). 337 (40%) of 853 patients had at least one protocol deviation in the study, of whom

172 (40%) of 426 were in the secukinumab group and 165 (39%) of 427 were in the adalimumab group. Major reasons for protocol deviations were use of prohibited concomitant medication and other deviations from Good Clinical Practice guidelines. Other reasons for protocol deviations included unmet selection criteria and treatment deviation. For further details of protocol deviations, see the appendix (p 24).

Outcomes

The primary outcome was the proportion of patients with at least 20% improvement in the ACR response criteria (ACR20) at week 52. Key secondary endpoints in order of the statistical hierarchy were Psoriasis Area and Severity Index (PASI) 90 response, ACR50 response, mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score, and resolution of enthesitis (based on Leeds Enthesitis Index [LEI] criteria) at week 52.

Prespecified exploratory endpoints assessed at week 52 were clinically relevant musculoskeletal and skin endpoints, which included the proportion of patients achieving a combined ACR50 and PASI 100 response, PASI 75 or 100 response, absolute PASI score of 3 or less, ACR70 response, psoriatic arthritis response criteria response, resolution of dactylitis, resolution of enthesitis (based on Spondyloarthritis Research Consortium of Canada [SPARCC] criteria), proportion of patients achieving Psoriatic Arthritis Disease Activity Score (PASDAS) low disease activity and remission, Disease Activity in Psoriatic Arthritis (DAPSA) low disease activity and remission, minimal disease activity, and very low disease activity response and quality-of-life questionnaires (HAQ-DI). Additional prespecified efficacy analyses in the subset of patients with psoriasis with body surface area greater than 10% or PASI of at least 10 were also done.

Safety analyses included all safety data reported up to and including the week 52 visit for each patient who received at least one dose of study drug. MedDRA version 22.0 was used for reporting adverse events.

Statistical analysis

The study was powered based on the planned analysis of patients achieving an ACR20 response at week 52. An ACR20 response rate of 50% for the TNF inhibitor-naive population without methotrexate use (monotherapy) was assumed for adalimumab based on observed week 48 response rate reported in a previous study.[19] The response to secukinumab was estimated to be 62% based on ACR20 response in the TNF inhibitor-naive monotherapy population from phase 3 studies.[6] With 425 patients per treatment group, we anticipated that there would be approximately 94% power to detect a treatment difference of around 12% (odds ratio [OR] 1·63) in ACR20 response rates at two-sided α=0·05 between secukinumab and adalimumab in the evaluation of the primary efficacy hypothesis at week 52.

	Secukinumab 300 mg (n=426)	Adalimumab 40 mg (n=427)	Total (n=853)
Age (years)	48·5 (12·38)	49·5 (12·44)	49·0 (12·41)
Sex			
Male	208 (49%)	229 (54%)	437 (51%)
Female	218 (51%)	198 (46%)	416 (49%)
Weight (kg)	83·5 (19·12)	84·1 (18·33)	83·8 (18·72)
Body-mass index (kg/m²)	28·8 (6·03)	28·9 (5·55)	28·8 (5·79)
Race			
White	402 (94%)	391 (92%)	793 (93%)
Asian	16 (4%)	20 (5%)	36 (4%)
Other or unknown	8 (2%)	16 (4%)	24 (3%)
No smoking status at baseline	333 (78%)	351 (82%)	684 (80%)
Systemic glucocorticoids use at randomisation	61 (14%)	58 (14%)	119 (14%)
Time since first diagnosis of psoriatic arthritis (years)	5·1 (7·60)	5·7 (7·29)	5·4 (7·45)
Baseline PASI score	10·6 (9·00)	10·0 (8·15)	10·3 (8·60)
Patients with psoriasis (BSA ≥3%)	215 (50%)	202 (47%)	417 (49%)
Patients with psoriasis (BSA >10% or PASI ≥10)	110 (26%)	101 (24%)	211 (25%)
Adjusted tender joint total score for psoriatic arthritis (78 joints)	19·4 (13·86)	20·6 (14·81)	20·0 (14·35)
Adjusted swollen joint total score for psoriatic arthritis (76 joints)	9·7 (7·30)	10·2 (7·86)	10·0 (7·58)
Patient's global assessment (0–100)	64·0 (19·67)	61·9 (20·75)	62·9 (20·23)
Physician's global assessment (0–100)	60·0 (17·12)	61·4 (15·92)	60·7 (16·54)
Psoriatic arthritis pain (0–100)	58·6 (23·49)	57·9 (22·42)	58·3 (22·95)
Health Assessment Questionnaire-Disability Index	1·3 (0·64)	1·2 (0·64)	1·3 (0·64)
CRP ≥10 mg/L	131 (31%)	128 (30%)	259 (30%)
Disease Activity Score 28-CRP	4·7 (1·00)	4·7 (0·94)	4·7 (0·97)
Presence of enthesitis (Leeds Enthesitis Index)	234 (55%)	264 (62%)	498 (58%)
Presence of enthesitis (Spondyloarthritis Research Consortium of Canada)	301 (71%)	330 (77%)	631 (74%)
Presence of dactylitis	130 (31%)	137 (32%)	267 (31%)

Data are mean (SD) or n (%). BSA=body surface area. CRP=C-reactive protein. PASI=Psoriasis Area Severity Index.

Table 1: **Baseline and disease characteristics of patients**

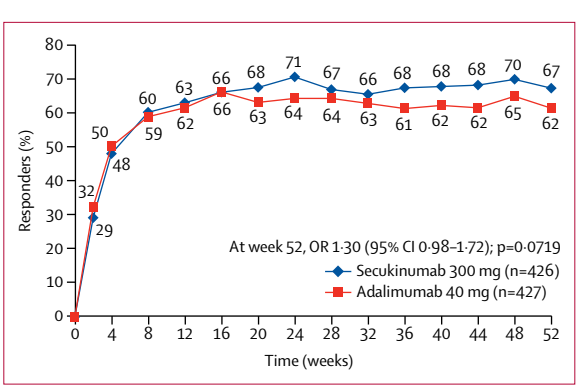

Figure 2: **ACR20 response rate through week 52 (multiple imputation)**
Unadjusted p values versus adalimumab are presented. Data were analysed using logistic regression. Patients who discontinued study treatment before or at week 50 or took csDMARDs after week 36 were considered non-responders for the visits after discontinuation or taking csDMARDs. Multiple imputation was used for all other missing data. csDMARD=conventional synthetic disease-modifying anti-rheumatic drugs. OR=odds ratio.

	Secukinumab 300 mg	Adalimumab 40 mg	Odds ratio (95% CI)	p value (unadjusted)*
Primary endpoint				
ACR20	67% (426)	62% (427)	1·30 (0·98 to 1·72)	0·0719
Prespecified sensitivity analysis using non-responder imputation				
ACR20	67% (426)	59% (427)	1·38 (1·04 to 1·83)	0·0239
Key secondary endpoints				
PASI 90	65% (215)	43% (202)	2·49 (1·67 to 3·71)	<0·0001
ACR50	49% (426)	45% (427)	1·18 (0·90 to 1·55)	0·2251
HAQ-DI score, change from baseline, mean (SE) [n]	−0·58 (0·03) [363]	−0·56 (0·03) [318]	−0·02† (−0·10 to 0·05)	0·5465
Resolution of enthesitis (based on Leeds Enthesitis Index)	61% (234)	54% (264)	1·30 (0·91 to 1·87)	0·1498
Combined endpoint				
ACR50 plus PASI100‡	31% (215)	19% (202)	1·85 (1·17 to 2·92)	0·0087
Exploratory endpoints				
Psoriatic arthritis endpoints				
Minimal disease activity (78/76 joints)	43% (426)	38% (427)	1·22 (0·93 to 1·61)	0·1498
Very low disease activity (78/76 joints)	18% (426)	17% (427)	1·10 (0·77 to 1·57)	0·6107
DAS28 CRP low disease activity	69% (426)	61% (427)	1·45 (1·09 to 1·95)	0·0118
DAPSA low disease activity and remission	62% (426)	53% (427)	1·41 (1·06 to 1·87)	0·0178
DAPSA-based remission	25% (426)	24% (427)	1·04 (0·76 to 1·42)	0·8252
DAS28 CRP-based remission	53% (426)	48% (427)	1·20 (0·91 to 1·59)	0·1922
ACR70	33% (426)	29% (427)	1·17 (0·87 to 1·57)	0·2950
Resolution of dactylitis	75% (130)	70% (137)	1·29 (0·75 to 2·22)	0·3560
Resolution of enthesitis (based on Spondyloarthritis Research Consortium of Canada)	53% (301)	50% (330)	1·11 (0·81 to 1·52)	0·5117
PASDAS-based remission	22% (425)	18% (427)	1·27 (0·90 to 1·79)	0·1708
PASDAS-based low disease activity and remission	51% (425)	44% (427)	1·31 (0·99 to 1·73)	0·0557
Psoriatic Artiritis Response Criteria	80% (426)	70% (427)	1·71 (1·24 to 2·34)	0·0009
Skin endpoints§				
PASI 75	79% (215)	61% (202)	2·33 (1·50 to 3·60)	0·0002
PASI 100	46% (215)	30% (202)	2·01 (1·34 to 3·03)	0·0007
Absolute PASI score ≤3	79% (215)	65% (202)	2·06 (1·32 to 3·22)	0·0015
Quality-of-life endpoints				
HAQ-DI ≥0·3	55% (426)	51% (427)	1·13 (0·85 to 1·49)	0·3984
HAQ-DI ≥0·35	55% (426)	51% (427)	1·13 (0·86 to 1·49)	0·3945

Data % (N), unless otherwise indicated. Binary variables, including the primary endpoint, were analysed using logistic regression. Patients who discontinued study treatment before or at week 50 or took csDMARDs after week 36 were considered non-responders for the visits after discontinuation or taking csDMARDs. Multiple imputation was used for all other missing data. The primary endpoint of ACR20, as part of the prespecified sensitivity analysis, was analysed using non-responder imputation for all other missing data. Continuous variables were analysed using mixed-effect model repeated measures. ACR=American College of Rheumatology. PASI=Psoriasis Area Severity Index. HAQ-DI=Health Assessment Questionnaire-Disability Index. DAS28=disease activity score based on 28 joint count. CRP=C-reactive protein. DAPSA=Disease Activity in Psoriatic Arthritis. PASDAS=Psoriatic Arthritis Disease Activity Score. csDMARDS=conventional synthetic disease-modifiying antirheumatic drugs. *Versus adalimumab. †Between-treatment difference in mean change from baseline for HAQ-DI is presented and n is the number of patients having values both at baseline and week 52. ‡Proportion of ACR50 responders among patients with psoriasis who have ≥3% body surface area affected at baseline and have achieved PASI 100 response. §PASI 75 and 100 responses and absolute PASI scores ≤3 are calculated in patients with psoriaris who have ≥3% body surface area affected at baseline.

Table 2: **Efficacy and health outcomes at week 52 in full analysis set**

The full analysis set used for efficacy analysis comprised all patients who were randomly assigned to study treatment. As per the intention-to-treat principle, patients were analysed according to the treatment to which they were randomly assigned. Psoriasis-related endpoints used the psoriasis subset, which included all patients in the full analysis set who had at least 3% of their body surface area affected by psoriasis at baseline. Enthesitis-related endpoints used the enthesitis subset, which included all patients in the full analysis set who had enthesitis based on LEI (as a key secondary endpoint) and based on SPARCC criteria (as an exploratory endpoint) at baseline.

We used a sequential hierarchical testing method to maintain the familywise type 1 error rate at 5% across the primary and ranked secondary endpoints. If the primary efficacy analysis was significant, secondary analyses were planned to be completed in the following sequence: ACR20, PASI 90, ACR50, HAQ-DI, and resolution of enthesitis. The inferential testing procedure only continued if the previous test was rejected at the two-sided 5% level. Subgroup analysis was tested independently from the hierarchical testing strategy.

The primary efficacy endpoint was defined as meeting the following three conditions: achieving an ACR20 response, with no permanent study treatment (secukinumab or adalimumab) discontinuation before or at week 50 (the last dosing visit), and no concomitant use of csDMARDs (including methotrexate) after week 36 (regardless of the time initiation of csDMARDs). A patient meeting all these conditions was regarded as a responder, otherwise they were considered non-responders. All secondary and exploratory binary endpoints were defined in the same way as the primary endpoint.

For analyses of binary endpoints, we computed ORs, 95% CIs, and p values for comparisons of secukinumab versus adalimumab from a logistic regression model, with treatment as a factor and baseline weight as a covariate.

For the primary endpoint and other binary endpoints, if a patient discontinued study treatment prematurely or took csDMARDs after week 36 they were considered a non-responder. If a patient neither discontinued study treatment prematurely nor took csDMARDs after week 36 but had all or some components missing that precluded the calculation of ACR20 response (eg, missed visits, electronic device malfunction, or site error), then missing data for these components were handled by multiple imputation. This method imputes missing data based on a patient's own observed data and observed data from similar patients in similar conditions. As a sensitivity analysis, non-responder imputation was specified to assess the effect of missing data. Non-responder imputation is a highly conservative method that assumes non-response for all missing data.

We evaluated between-group differences in continuous endpoints using a mixed-effect model repeated measures

approach, with missing data assumed to be missing at random. Treatment and assessment visit were included in the model as factors. Weight and baseline values of the endpoints were included in the model as continuous covariates. Treatment by analysis visit and baseline score by analysis visit were interaction terms, and an unstructured covariance structure was assumed.

For continuous efficacy endpoints, data for patients who discontinued study treatment before week 50 or took csDMARDs after week 36 were set to missing for the visits after discontinuation or taking csDMARDs.

Safety endpoints were assessed for all patients who received at least one dose of study drug and were summarised descriptively for data reported up to and including each patient's week 52 visit at the time of the week 52 database lock (Oct 21, 2019).

Analyses were done with SAS version 9.4. The trial is registered at ClinicalTrials.gov, NCT02745080.

Role of the funding source

The study was designed by the funder, Novartis, in collaboration with the authors. Data were collected in accordance with Good Clinical Practice guidelines by the study investigators and were analysed by the funder. All authors contributed to interpretation of the data and had access to the full datasets. Statistical analyses were done by statisticians employed by the funder and were reviewed by all authors. Agreements between the funder and the investigators included provisions relating to confidentiality of the study data. Writing support for the manuscript was provided by a medical writer from Novartis, India, and funded by the funder. All authors vouch for the accuracy and completeness of the data and analyses, as well as for the fidelity of this report to the trial protocol, which is available from the funder. All authors had the final responsibility for the decision to submit the manuscript for publication.

Results

Between April 3, 2017, and Aug 23, 2018, we randomly assigned 853 patients to receive secukinumab (n=426) or adalimumab (n=427). 709 (83%) of 853 patients completed week 52 of the study (figure 1), of whom 691 (81%) received the last study treatment at week 50 (appendix p 20). 61 (14%) of 426 patients in the secukinumab group discontinued treatment by week 52 versus 101 (24%) of 427 patients in the adalimumab group. Major reasons for discontinuation of treatment were adverse events (15 [4%] of 426 patients in the secukinumab group *vs* 30 [7%] of 427 patients in the adalimumab group), lack of efficacy (15 [4%] of 426 patients in the secukinumab group *vs* 32 [7%] of 427 patients in the adalimumab group), and patient or guardian decision (23 [5%] of 426 patients in the secukinumab group *vs* 35 [8%] of 427 patients in the adalimumab group). A Kaplan-Meier curve for time to study treatment discontinuation is shown in the appendix (p 21), indicating a higher proportion of patients being retained for a longer duration on secukinumab versus adalimumab until the last dosing visit at week 50 (p=0·0005).

Baseline demographics and disease characteristics were similar across the secukinumab and adalimumab groups, except for the proportion of female patients and patients with enthesitis as defined by LEI (table 1).

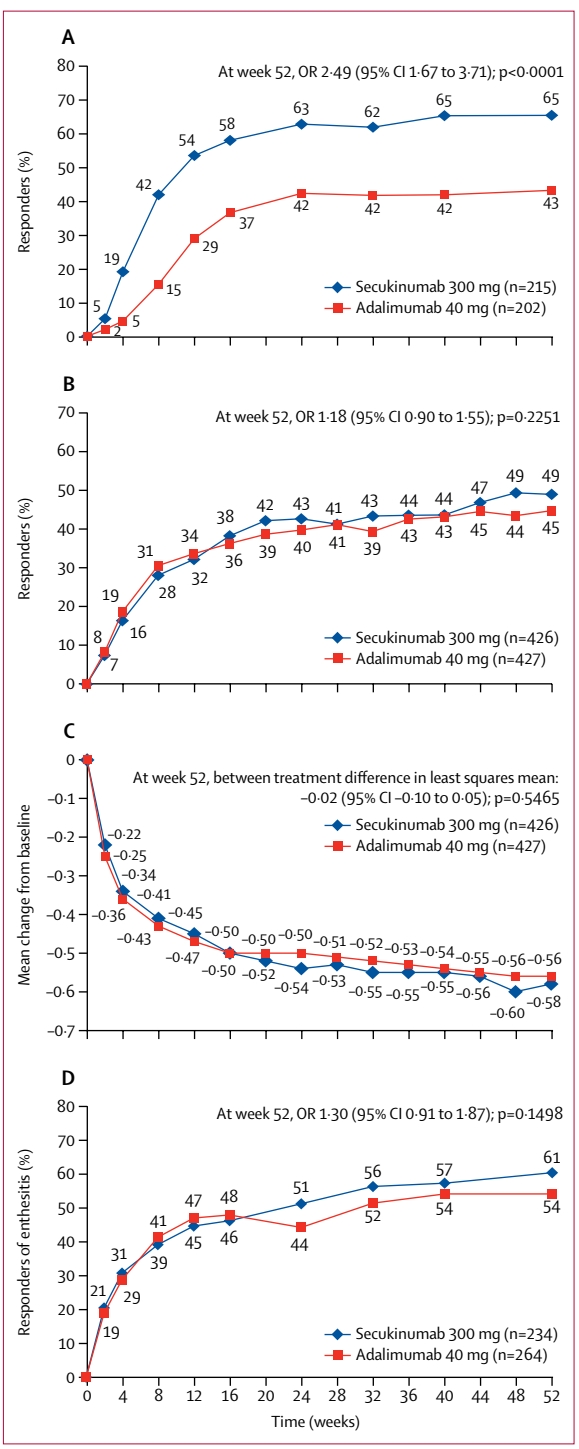

Figure 3: **Key secondary endpoints up to week 52**
Patients who discontinued study treatment before or at week 50 or took csDMARDs after week 36 were considered non-responders for the visits after discontinuation or taking csDMARDs. Multiple imputation was used for all other missing data for binary variables (PASI 90, ACR50, and resolution of enthesitis based on LEI). Unadjusted p values are presented versus adalimumab. (A) PASI 90 response. PASI reported only in patients with at least 3% body surface area affected with psoriasis at baseline. (B) ACR50 response. (C) Mean change from baseline in Health Assessment Quality-Disability Index score Least squares means are from mixed-effect model repeated measures with treatment group, analysis visit as factors, weight, and baseline score as covariates, and treatment by analysis visit, and baseline score by analysis visit as interaction terms. (D) Resolution of enthesitis is reported in number of patients with available enthesitis data at baseline (LEI criteria). csDMARD=conventional synthetic disease-modifying anti-rheumatic drugs. OR=odds ratio. PASI=psoriasis area severity index. ACR=American College of Rheumatology. LEI=Leeds Enthesitis Index.

	Secukinumab 300 mg (n=426)	Adalimumab 40 mg (n=427)
Duration of exposure (days)	351·7 (77·9)	332·9 (94·2)
Number of patients with any adverse event	330 (77%)	338 (79%)
Number of patients with serious or other clinically significant events		
Death* (n)	1	0
Non-fatal serious adverse events	32 (8%)	28 (7%)
Discontinued study treatment because of adverse event	17 (4%)	32 (7%)
Adverse events of special interest		
Infections and infestations (system organ class)	237 (56%)	234 (55%)
Serious infections	7 (2%)	6 (1%)
Candida infections (high-level term)	16 (4%)	7 (2%)
Viral infectious disorders (high-level group term)	66 (15%)	65 (15%)
Injection-site reactions (high-level term)	17 (4%)	47 (11%)
Hypersensitivity (standardised MedDRA query; narrow)	39 (9%)	60 (14%)
Major adverse cardiac event (Novartis MedDRA query)	2 (<1%)	0
Inflammatory bowel disease (Novartis MedDRA query; narrow term)†	2 (<1%)	0
Crohn's disease (preferred term)	1† (<1%)	0
Ulcerative colitis (preferred term)	2† (<1%)	0
Malignancies	2 (<1%)	3 (1%)
Most frequent treatment-emergent adverse events		
Nasopharyngitis	81 (19%)	80 (19%)
Upper respiratory tract infection	41 (10%)	49 (11%)
Headache	35 (8%)	32 (7%)
Diarrhoea	31 (7%)	35 (8%)
Hypertension	27 (6%)	23 (5%)
Oropharyngeal pain	25 (6%)	15 (4%)
Psoriasis	24 (6%)	25 (6%)
Arthralgia	23 (5%)	29 (7%)
Psoriatic arthropathy	20 (5%)	26 (6%)
Back pain	14 (3%)	31 (7%)
Bronchitis	14 (3%)	23 (5%)
Rash	8 (2%)	21 (5%)
Injection site reactions	4 (1%)	28 (7%)

Data are mean (SD) or n (%), unless otherwise indicated. n is the number of patients with events. MedDRA=Medical Dictionary for Regulatory Activities. *A 53-year-old man entered the study without any reported medical history or active medical conditions. On study day 85, this patient had severe abdominal pain considered a serious adverse event, which led to discontinuation of secukinumab and the study (last dose study day 70; total of six 300 mg doses). The patient was subsequently diagnosed with colon cancer, and died on study day 146. This event was assessed as not related to study drug by the investigator. †One patient was diagnosed with both Crohn's disease and ulcerative colitis.

Table 3: **Safety summary at week 52 in safety set**

357 (84%) of 426 patients in the secukinumab group and 371 (87%) of 427 patients in the adalimumab group were previously exposed to methotrexate.

The primary endpoint of superiority of secukinumab versus adalimumab for ACR20 response at week 52 was not met. 67% of patients in the secukinumab group has an ACR20 response at week 52 versus 62% in the adalimumab group (OR 1·30, 95% CI 0·98–1·72; p=0·0719; figure 2, table 2). Three patients in the secukinumab group and ten patients in adalimumab group with partial or all missing values of the ACR components at baseline or week 52 (not because of treatment or study discontinuation) had values imputed using multiple imputation. In the prespecified sensitivity analysis using non-responder imputation, these 13 patients were imputed as non-responders and ACR20 response at week 52 was reported in 285 (67%) of 426 patients in the secukinumab group and 254 (59%) of 427 patients in the adalimumab group (OR 1·38, 95% CI 1·04–1·83; p=0·0239; table 2).

As the superiority of secukinumab versus adalimumab was not established for the primary endpoint, key secondary endpoints in the hierarchy were not formally tested for statistical significance. Therefore, we present unadjusted p values (without adjusting for multiplicity) and ORs with 95% CIs for key secondary endpoints (table 2; figure 3).

In prespecified exploratory analyses, a higher proportion of patients in the secukinumab group versus the adalimumab group achieved combined joint and skin response (simultaneous ACR50 and PASI 100 response), specific skin outcomes (PASI 75 response, PASI 100 response, absolute PASI score ≤3), low disease activity score (disease activity score based on 28 joint count C-reactive protein low disease activity, DAPSA-based low disease and remission, PASDAS-based low disease activity and remission, and Psoriatic Arthritis Response Criteria responses (table 2).

Overall, 211 (25%) of 853 patients had psoriasis with body surface area greater than 10% or PASI of at least 10. In this subset of patients, ACR20 and PASI 90 responses with secukinumab versus adalimumab were seen in 76% versus 68% of patients and 69% versus 42% of patients, respectively. The data for efficacy outcomes reported in this subset of patients were consistent with the overall study population (appendix p 22).

The safety profiles of secukinumab and adalimumab were consistent with previous reports.[6,20] Over the entire treatment period, the mean exposure to secukinumab was 351·7 days (SD 77·9) and to adalimumab was 332·9 days (94·2). Treatment-emergent adverse events occurred in 330 (77%) of 426 patients in the secukinumab group and 338 (79%) of 427 patients in the adalimumab group (table 3).

Major adverse cardiovascular events were reported in two (<1%) patients in the secukinumab group (a male patient with a pre-existing medical history of diabetes, hypertension, and dyslipidaemia, and ongoing ischaemic heart disease with previous stent insertion had acute myocardial infarction and a male patient, a current smoker with a pre-existing medical history of hypertension, had a myocardial infarction). One patient in the adalimumab group had acute cardiac failure that required hospitalisation. Inflammatory bowel disease (IBD) was reported in two patients in the secukinumab group—one patient was diagnosed with both ulcerative colitis and Crohn's disease and the other had ulcerative colitis. Both IBD cases were flares in patients with a pre-existing medical history of IBD. Two cases of malignancy were reported in the secukinumab group—one patient

had colon cancer (day 85) and the other was diagnosed with plasma cell myeloma (day 201). Three cases of malignancy were reported in the adalimumab group, a synovial sarcoma (day 361), intraductal papillary carcinoma of the pancreas (day 85), and non-Hodgkin lymphoma (day 222). All cases of malignancy led to treatment discontinuation.

One death was reported in the secukinumab group. The patient had severe abdominal pain and discontinued the study on day 85 after receiving six doses of secukinumab. The patient died after study discontinuation on day 146 due to colon cancer assessed as not related to study drug by the investigator.

Discussion

With increased availability of approved medicines that have distinct mechanisms of action, head-to-head trials can be useful to help guide clinical decision making in the management of psoriatic arthritis after csDMARD (including methotrexate) failure, intolerance, or contraindication.[3,21] To our knowledge, EXCEED is the first head-to-head, double-blind, randomised trial to compare secukinumab and adalimumab, and tested a musculoskeletal primary endpoint of ACR20 response in psoriatic arthritis. This trial addresses an important gap in knowledge that informs the initiation of biological treatment in patients with psoriatic arthritis in the context of biological monotherapy. Pooled FUTURE 2–5 studies show that secukinumab 300 mg provides greater efficacy than does secukinumab 150 mg or placebo and long-term maintenance of response in biological-naive patients irrespective of concomitant methotrexate use; hence, we used secukinumab 300 mg in this study.[22] The results of the pre-specified sensitivity analysis also showed higher ACR20 response rates at week 52 versus adalimumab.

Baseline demographics and disease characteristics were generally similar between the secukinumab group and adalimumab group; however, the proportion of female patients was higher in the secukinumab group than in the adalimumab group. Several reports have shown that female patients have lower treatment response rates in psoriatic arthritis than do male patients.[23]

It is becoming increasingly clear that different tissue compartments in psoriatic arthritis might not be driven by identical pathogenetic pathways. A cutaneous psoriasis study showed superiority of IL-17A inhibition with secukinumab compared with etanercept, a TNF inhibitor, in a head-to-head trial.[9]

A 2020 open-label, head-to-head study of the IL-17A inhibitor ixekizumab versus adalimumab reported that ixekizumab was superior in achievement of simultaneous improvement of joint and skin disease (combined ACR50 and PASI 100 response) in patients with psoriatic arthritis and inadequate response to csDMARDs.[24] The current study has several important elements. It was fully blinded, minimising the potential bias and effect of knowledge of treatment allocation on reporting of outcomes. The study included patients who more closely reflect patients with psoriatic arthritis who visit the rheumatology clinic, as the patients predominantly had articulatar symptoms. We investigated biological monotherapy, representing a common, clinically relevant scenario given either primary methotrexate intolerance or prevalence of metabolic syndrome and hepatosteatosis in psoriatic arthritis, both of which pose challenges for the use of methotrexate.[13–15] Importantly, we evaluated musculoskeletal disease as the primary outcome, thereby removing the influence of cutaneous responses on interpretation of the results. Moreover, our primary outcome directly addresses a key research question in psoriatic arthritis management, namely whether IL-17A or TNF inhibition confer musculoskeletal advantage. However, we recognise that improvements in both musculoskeletal and skin manifestations are considered essential for optimising overall quality of life in psoriatic arthritis.[25] Notably, secukinumab also showed a higher combined ACR50 and PASI 100 response, PASI 75 response, and PASI 100 responses compared with adalimumab in the current study. Overall, the data suggest that IL-17A inhibitors could offer a more robust proposition to manage the entirety of the clinical manifestations of patients with psoriatic arthritis.

EULAR recommends a treat-to-target approach for patients with psoriatic arthritis for achieving low disease activity or remission as an important goal of treatment, which has been shown to improve physician-reported and patient-reported outcomes in those with recent onset of psoriatic arthritis.[26] The heterogeneous manifestations of psoriatic arthritis are captured in several composite definitions that encompass clinically important aspects, such as synovitis, psoriasis, enthesitis, pain, patient-assessed global disease activity, and physical function. One such composite definition, DAPSA, primarily focuses on peripheral arthritis, and does not include other psoriatic arthritis manifestations such as psoriasis, axial disease, nail disease, dactylitis, or enthesitis.[27] Secukinumab showed numerically higher efficacy compared with adalimumab across musculoskeletal endpoints and composite indices including DAPSA low disease activity, PASDAS low disease activity, minimal disease activity, and Psoriatic Arthritis Response Criteria response. A higher proportion of patients treated with secukinumab versus adalimumab achieved the stringent outcome of DAPSA low disease activity and remission, suggesting that improvements with secukinumab were driven primarily by musculoskeletal outcomes.

There were fewer overall discontinuations with secukinumab compared with adalimumab during the study. Higher proportions of patients discontinued adalimumab because of loss of efficacy, adverse events, and acute injection site reactions. Injection site reactions (including injection site pain) were higher with citrate-free adalimumab formulation, as shown in previous

studies in other indications.[28] The rates of IBD and candidiasis reported in this study for secukinumab were consistent with previously reported data for IL-17A inhibitors.[24,29] Overall, the safety profiles of both bDMARDs were consistent with those published in previous studies.[6,20,29,30]

Management of psoriatic arthritis in the clinical setting should be targeted at the disease domains (peripheral arthritis, axial disease, dactylitis, enthesitis, skin psoriasis, and nail psoriasis) that are active in, and important to, individual patients. Although there is evidence suggesting that IL-17A, IL-12/23p40, and IL-23p19 inhibitors have high efficacy in plaque psoriasis, the current study provides evidence for efficacy in musculoskeletal disease.

The monotherapy design of this study might limit the generalisation of its findings to the entire population, as concomitant methotrexate is widely used in psoriatic arthritis. Another limitation of this study is the lack of comparative data on inhibition of radiographic progression. Given the different treatment discontinuation rates between secukinumab and adalimumab, the underlying assumption behind the mixed model repeated measures (ie, missing at random) warrants further investigation. The influence of sex on efficacy of treatment also needs further analysis.

In conclusion, secukinumab did not meet statistical significance for superiority versus adalimumab in the primary endpoint of ACR20 response at week 52. However, secukinumab was associated with a higher treatment retention rate than was adalimumab and provided numerically higher clinical responses across musculoskeletal endpoints, skin endpoints, and composite indices at week 52. The safety profiles of secukinumab and adalimumab were consistent with previous reports. This study presents a considerable volume of comparative efficacy and safety data on two biological agents with different mechanisms of action in the treatment of patients with psoriatic arthritis.

Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship for this Article, take responsibility for the integrity of the work as a whole, were involved in drafting and critical review of the manuscript, and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work. SM, LP, IBM, PJM, AK, CR, and PN designed and conceived the study. FB, PN, JGM, PG, TK, and ABG interpreted the data. PP and KD acquired and analysed the data. RM analysed the data.

Declaration of interests

IBM declares research grants, consultation fees, or speaker honoraria from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB. FB declares research grants from Pfizer, Janssen, Chugai, Celgene, and Roche; consultation fees from Pfizer, AbbVie, Sanofi, Lilly, Novartis, Genzyme, Boehringer, Janssen, Merck Sharp & Dohme, Celgene, Roche, and Chugai; and investigator fees from Lilly. PJM reports grants or research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Galapagos, Genentech, Gilead, Janssen, Lilly, Merck, Novartis, Pfizer, SUN Pharma, and UCB; consultancy for AbbVie, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Galapagos, Celgene, Genentech, Gilead, Janssen, Lilly, Novartis, Pfizer, SUN Pharma, and UCB; and speakers bureau fees from AbbVie, Amgen, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB. AK reports consultancy fees and grants or research support from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, and UCB. CR reports research grants from AbbVie, Amgen, and UCB and consultancy for AbbVie, Amgen, UCB, Novartis, Pfizer, Lilly, Janssen, and Bristol-Myers Squibb. PN reports research grants for clinical trials and honoraria for lectures and advice from Novartis, Abbvie, Roche, Pfizer, Bristol-Myers Squibb, Janssen, Celgene, UCB, Lilly, Merck Sharp & Dohme, Sanofi, and Gilead. JGM reports research grants, consultation fees, or speaker honoraria from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, and Pfizer. PG reports research grants, consultation fees, or speaker honoraria from AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Chugai, Janssen, Lilly, Medac, Merck Sharp & Dohme, Nordic Pharma, Novartis, Pfizer, Sanofi, and UCB. TK reports research grants, consultation fees, or speaker honoraria from AbbVie, Bristol-Myers Squibb, Janssen, Lilly, Novartis, Pfizer, BIOCAD, and UCB. ABG reports research grants from Janssen, Incyte, Novartis, XBiotech, UCB, and Boerhinger Ingelheim, and consulting fees from Janssen, Incyte, Novartis, XBiotech, UCB, Boerhinger Ingelheim, Celgene, Beiesdorf, Bristol-Myers Squibb, Abbvie, Lilly, SUN Pharma, and Avotres Therapeutics. RM, PP, SM, and LP are shareholders and employees of Novartis. KD is an employee of Novartis.

Data sharing

The datasets generated and analysed during the current study are not publicly available. Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved based on scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. The data can be requested from the corresponding author of the manuscript. The protocol can be made available on request by contacting the corresponding author.

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